

ASSOCIATION OF CHRONIC LYME ARTHRITIS WITH HLA-DR4 AND HLA-DR2 ALLELES

ALLEN C. STEERE, M.D., EDWARD DWYER, M.D., AND ROBERT WINCHESTER, M.D.

Abstract Background and Methods. A small percentage of patients infected with *Borrelia burgdorferi* have chronic Lyme arthritis that does not respond to antibiotic therapy. To learn whether genetically determined variations in the host immune response might account for such outcomes, we determined the immunogenetic profiles of 130 patients with various manifestations of Lyme disease.

Results. Of the 80 patients with arthritis, 57 percent of those with chronic arthritis (12 to 48 months in duration) had the HLA-DR4 specificity; only 23 percent of those with arthritis of moderate duration (6 to 11 months) and only 9 percent of those with arthritis of short duration (1 to 5 months) had this specificity ($P = 0.003$). After the HLA-DR4-positive patients were excluded from each group, a secondary association was noted with HLA-DR2, which was found in 75 percent of the remaining patients with chronic arthritis and in 50 percent of those with arthritis of

moderate duration, but in only 20 percent of those with arthritis of short duration ($P = 0.023$). Altogether, 25 of the 28 patients with chronic arthritis (89 percent) had HLA-DR2 or HLA-DR4, or both, as compared with 27 percent of those with arthritis of short duration (relative risk, 22; $P = 0.00006$). These HLA specificities appeared to act as independent, dominant markers of susceptibility. Nucleotide-sequence typing, performed in five patients with chronic arthritis, identified the HLA-DR2 allele as Dw2 (DR β 1*1501), and the HLA-DR4 alleles as Dw4, Dw14, and Dw13 (DR β 1*0401, DR β 1*0404, and DR β 1*0403, respectively). The presence of HLA-DR4 in patients with arthritis was associated with a lack of response to antibiotic therapy ($P = 0.01$).

Conclusions. Particular Class II major histocompatibility genes determine a host immune response to *B. burgdorferi* that results in chronic arthritis and lack of response to antibiotic therapy. (N Engl J Med 1990; 323:219-23.)

LYME disease, which is caused by the tick-borne spirochete *Borrelia burgdorferi*, often begins with a characteristic skin lesion, erythema migrans, and is commonly followed by neurologic, cardiac, or joint abnormalities of variable duration.¹ The involvement of the joints, which is seen in about 80 percent of patients, often begins with migratory joint pain and is frequently followed months later by brief attacks of oligoarthritis.² During the second and third years of illness, the episodes of arthritis may last longer, and in about 10 percent of patients joint involvement becomes chronic, sometimes with erosion of cartilage and bone.^{2,3} The synovial lesions in such patients are similar to those seen in the other types of chronic inflammatory arthritis, including rheumatoid arthritis.^{4,5} In patients who later have arthritis, *B. burgdorferi* probably spreads to the joints early in the illness,² but the fact that only a small percentage have chronic arthritis suggests that host factors determine the severity and duration of arthritis. Lyme arthritis can usually be treated successfully with antibiotic therapy.^{6,7} However, regardless of the antibiotic used and the number of courses given, in some patients the arthritis does not respond to treatment.

Susceptibility to a number of diseases with autoimmune features is associated with HLA specificities encoded by certain Class II, D-locus alleles of the major histocompatibility complex. The Class II mole-

cules, expressed primarily on B cells and macrophages, bind and present antigen to T helper cells, which then initiate an immune response against these antigens. Genetic variations in the structure of Class II molecules are thought to influence the development of autoimmune responses, either by determining the type and manner of antigen binding or by influencing the composition of the T-cell repertoire in the development of self-tolerance during thymic maturation.

In an early study of 10 patients with chronic Lyme arthritis, 7 had HLA-DR2, and 4 had HLA-DR4,⁸ suggesting that the chronic joint involvement of this infectious disease might have an immunogenetic basis. To examine this hypothesis further, we determined the immunogenetic profiles of 130 patients with various manifestations of Lyme disease.

METHODS

Selection of Patients

In 1983, in the first phase of the study, we selected 75 patients who had had skin, neurologic, or joint manifestations of Lyme disease for immunogenetic testing. Among them, 30 patients had had erythema migrans but no other manifestations of the illness; 20 patients had had Lyme meningitis, sometimes accompanied by cranial neuritis or radiculoneuritis; and 25 patients had had brief or prolonged episodes of Lyme arthritis. These groups included most of the patients we had seen in these categories who had not been treated with antibiotic therapy. From January 1985 through June 1987, in the second phase of the study, we tested all 55 patients with Lyme arthritis seen at Yale University at the time of their entry into a study of antibiotic treatment. The patients with arthritis were subdivided into three groups according to the length of the longest period of continual joint involvement — those who had arthritis of short duration (1 to 5 months), those who had arthritis of moderate duration (6 to 11 months), and those who had chronic arthritis (12 to 48 months). The study was approved by the Human Investigations Committee of Yale University, and informed consent was obtained from each patient.

All the patients in both phases of the study were white and came from five states along the northeastern coast of the United States.

From the Division of Rheumatology/Immunology, New England Medical Center, Tufts University School of Medicine, Boston (A.C.S.), and the Hospital for Joint Diseases and the Division of Rheumatology, Department of Medicine, New York University Medical Center, New York (E.D., R.W.). Address reprint requests to Dr. Steere at the Division of Rheumatology/Immunology, New England Medical Center, NEMC 406, 750 Washington St., Boston, MA 02111.

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Their ages ranged from 7 to 72 years (median, 34); 72 were male, and 58 female. All had elevated titers of serum IgM or IgG antibody to *B. burgdorferi*, measured as previously described.^{9,10} For comparison, we studied 86 normal subjects, 53 men and 33 women, ranging in age from 18 to 54 years (median, 31), at the New York University Medical School. These subjects underwent HLA typing at the same time and with use of the same reagents as the patients with Lyme disease.

HLA-Typing Procedures

The HLA-A, B, C, DR, and DQ specificities were identified by standard lymphocyte-microcytotoxicity testing¹¹ with use of a panel of local and exchanged alloantisera.¹² In five patients with chronic Lyme arthritis who were typed as HLA-DR4 or HLA-DR2, the complementary DNA of the DR β chain was sequenced. In these patients, 5 μ g of total RNA was isolated from peripheral-blood mononuclear cells, and first-strand synthesis of complementary DNA was carried out with use of reverse transcriptase in the presence of primers (5', codons -12 to -6; 3', codons 105 to 112).¹³ After the addition of *Taq* polymerase, 25 cycles of polymerase-chain-reaction amplification were performed in a DNA thermal cycler (Perkin-Elmer-Cetus), as previously described.¹⁴ The amplified product was run on a gel, and the appropriate band was cloned into the plasmid pUC18 using *Sst*I and *Sma*I restriction-enzyme sites. After transfection of XLI-blue *Escherichia coli*, 10 to 50 colonies with inserts were selected and grown. The constructs were characterized first by restriction-enzyme digestion and then sequenced by the dideoxy method.¹⁵

Statistical Analysis

For statistical analysis, the comparisons of HLA types in patients or normal subjects were made in two-by-two tables, from which the odds ratios were calculated. We have expressed the odds ratios in terms of the relative risk, as is customary in this field. The statistical significance of the relative risk was calculated by Fisher's exact test (two-tailed). In an attempt to nullify the possibility of chance association with a given allele, P values were multiplied by the number of specificities tested at each locus: seven for DR and three for DQ.

RESULTS

Of the 75 selected patients with different manifestations of Lyme disease whom we tested in the first phase of the study, the frequencies of HLA-A, B, C, and D specificities in those with erythema migrans alone, meningitis, or arthritis were similar to those in the 86 normal subjects. However, when the group with joint involvement was stratified according to the duration of arthritis, 4 of the 9 patients with chronic arthritis (44 percent) but none of the 16 patients who had had shorter periods of arthritis had the HLA-DR4 specificity. In order to increase the size of the arthritis group and to avoid selection bias, we next tested all 55 patients with Lyme arthritis whom we saw during a subsequent 1½-year period, at the time of their entry into antibiotic-treatment studies. In this larger, independent, unselected series, the frequency of HLA-DR4 was again increased in the 19 patients with chronic arthritis as compared with the 36 patients with shorter episodes of arthritis. Since the results from both phases of the study were similar, they are presented together here.

Immunogenetic Profiles of Patients with Lyme Arthritis

Among the 80 patients in both groups who had Lyme arthritis, the HLA-DR4 specificity was found in

57 percent of those with chronic arthritis (of 12 to 48 months' duration), in 23 percent of those with arthritis of moderate duration (6 to 11 months), and in only 9 percent of those with arthritis of short duration (1 to 5 months) (Table 1). Therefore, the frequency of HLA-DR4 was significantly greater in patients with chronic arthritis than in those with arthritis of short duration (57 percent vs. 9 percent; relative risk, 13; $P < 0.003$) or the normal subjects (57 percent vs. 31 percent; relative risk, 3; $P < 0.01$). All 16 patients with chronic arthritis who had HLA-DR4 were heterozygous at the DR locus. Five had HLA-DR4 and HLA-DR3, four had HLA-DR4 and HLA-DR2, three had HLA-DR4 and HLA-DR1, and the remaining four had HLA-DR4 in association with a different DR specificity.

A secondary association was noted with the HLA-DR2 specificity. This specificity was found in 43 percent of the patients with chronic arthritis and in 40 percent of those with arthritis of moderate duration, but in only 18 percent of those with arthritis of short duration (Table 1). Among patients with arthritis of moderate duration, the frequency of HLA-DR2 was higher than that of any other specificity, including HLA-DR4. After the exclusion of the HLA-DR4-positive patients in each group, the frequency of HLA-DR2 was significantly higher among the remaining patients with chronic arthritis than among those with arthritis of short duration (75 percent vs. 20 percent; relative risk, 12; $P = 0.023$) or the normal subjects (75 percent vs. 36 percent; relative risk, 5; $P = 0.02$). Taken together, 25 of the 28 patients with chronic arthritis had HLA-DR2, HLA-DR4, or both, as compared with only 6 of the 22 patients with arthritis of short duration (89 percent vs. 27 percent; relative risk, 22; $P = 0.00006$). Among the remaining three patients with chronic arthritis, two had HLA-DR1 alone, and one had HLA-DR3 and HLA-DR7.

During the second phase of the study, it was also possible to test for HLA-DRw52 and DRw53 and for the DQ specificities. Fourteen of the 16 patients with arthritis of short duration (88 percent) had HLA-DRw52, which is associated with HLA-DR3, -5, -w6, and -8; no patient with chronic arthritis had HLA-DRw6. In the above analysis, these specificities were independently associated with a lack of susceptibility to chronic arthritis. The frequency of HLA-DRw52 was significantly higher among patients with arthritis of short duration than among those with chronic arthritis (88 percent vs. 37 percent; relative risk, 0.05; $P = 0.003$) or those with arthritis of moderate duration (88 percent vs. 40 percent; relative risk, 0.1; $P = 0.005$) (Table 1). In contrast, the frequency of HLA-DRw53, which is associated with HLA-DR4, -7, and -9, tended to be higher among those with chronic arthritis, but this difference was not statistically significant — presumably because of the negative association of HLA-DR7 with chronic arthritis. The fre-

Table 1. Frequency of HLA-DR Specificities in 80 Patients with Lyme Arthritis and 86 Normal Subjects.

SPECIFICITY	NORMAL SUBJECTS (N = 86)	DURATION OF LYME ARTHRITIS*		
		SHORT (N = 22)	MODERATE (N = 30)	CHRONIC (N = 28)
		percent		
HLA-DR1	29	18	20	21
HLA-DR2	26	18	40	43
HLA-DR3	17	23	13	29
HLA-DR4	31	9	23	57†
HLA-DR5	28	32	20	14
HLA-DRw6	10	18	10	0
HLA-DR7	22	18	17	11
HLA-DR2 or HLA-DR4	53	27	63	89‡
HLA-DRw52	62	88§	40	37
HLA-DRw53	52	31	50	68
HLA-DQw1	56	69	60	53
HLA-DQw2	30	38	20	32
HLA-DQw3	32	63	55	74¶

*For the HLA-DRw52 and -w53 and HLA-DQ specificities, the numbers tested were as follows: short duration, n = 16; moderate duration, n = 20; chronic, n = 19.

†P = 0.003 for the comparison between patients with chronic arthritis and those with arthritis of short duration; P = 0.1 for the comparison between patients with chronic arthritis and normal subjects.

‡P = 0.00006 for the comparison between patients with chronic arthritis and those with arthritis of short duration; P = 0.002 for the comparison between patients with chronic arthritis and normal subjects.

§P = 0.003 for the comparison between patients with arthritis of short duration and those with chronic arthritis; P = 0.005 for the comparison between patients with arthritis of short duration and those with arthritis of moderate duration.

¶P = 0.003 for the comparison between patients with chronic arthritis and normal subjects.

quency of HLA-DQw3, which is associated with HLA-DR4 and -5, was higher in each group of patients with arthritis than among the normal subjects, but the differences were statistically significant only for patients with chronic arthritis as compared with normal subjects (74 percent vs. 32 percent; relative risk, 6; P = 0.003).

The frequencies of the HLA-A, B, and C specificities were not significantly different among the three groups of patients with Lyme arthritis. Of the 80 patients, 4 had HLA-B27, 3 of whom had chronic arthritis, but none had other manifestations of Reiter's syndrome or sacroiliitis. HLA-B7, a specificity that cross-reacts with HLA-B27, was found in 43 percent of the patients with chronic arthritis and in 37 percent of those with arthritis of short duration.

Nucleotide-Sequence Typing

To identify the alleles encoding the HLA-DR4 or DR2 specificity, we sequenced the genes that determine these specificities in five selected patients with chronic arthritis (Table 2). Three patients had the HLA-Dw14 or Dw4 allele (DRβ1*0404 or DRβ1*0401) encoding the DR4 specificity. A fourth patient had the HLA-Dw13 allele of DR4 (DRβ1*0403), but he also had the HLA-Dw2 allele of

DR2 (DRβ1*1501). The fifth patient also had the HLA-Dw2 allele of DR2.

DR Phenotypes and Response to Treatment

Of the 80 patients with Lyme arthritis, 60 were treated for their arthritis with antibiotic therapy. In 22 of the 60 patients, designated as responders, the arthritis improved during treatment and resolved completely within three months. The remaining 38 patients, classified as nonresponders, did not improve during treatment and continued to have joint involvement for more than three months thereafter. The age and sex of the patients, the duration of arthritis before treatment, and the antibiotics given were similar in the two groups. Of the 22 HLA-DR4-positive patients who were treated with antibiotics, the arthritis responded to treatment in only 2 (Table 3). Only the presence of HLA-DR4 was significantly associated with the failure of treatment (P = 0.01).

DISCUSSION

These results provide evidence that chronic Lyme arthritis has an immunogenetic basis involving the HLA-DR4 specificity and, secondarily, HLA-DR2. Although 25 of the 28 patients with chronic arthritis had HLA-DR4 or DR2, only 3 had both. This is approximately the number that would be expected on the basis of the estimated gene frequencies in these patients. This similarity suggests that HLA-DR4 and DR2 alleles act as independent, dominant markers of susceptibility and that the presence of both does not confer additional risk.

Several European studies have also found an association between HLA-DR2 and DR4 and certain other manifestations of Lyme disease. In Czechoslovakia, in a study of 32 patients with meningopolyneuritis, 56 percent had HLA-DR2, and 46 percent had HLA-DR4.¹⁵ In Vienna, of 22 patients with acrodermatitis, 52 percent had HLA-DR2.¹⁶ However, in two other European studies, the frequency of HLA-DR2 or DR4 was not increased in patients with meningopolyneuritis or acrodermatitis.^{17,18} Borrelial encephalomyelitis, a newly described late neurologic manifestation of Lyme disease,¹⁹ may resemble multiple sclerosis, which is also associated with an increased frequency of HLA-DR2.²⁰ It is not yet

Table 2. Nucleotide-Sequence Typing of the HLA-DRβ Chain in Five Representative Patients with Chronic Lyme Arthritis.

PATIENT NO.	RESULTS	
	SEROLOGIC TYPING	NUCLEOTIDE-SEQUENCE TYPING
1	DR1, DR4	DR1, Dw4 (DRβ1*0401)
2	DR2, DR4	Dw2, Dw14 (DRβ1*1501, 0404)
3	DR3, DR4	DR3, Dw14 (DRβ1*0404)
4	DR2, DR4	Dw2, Dw13 (DRβ1*1501, 0403)
5	DR2, DR3	Dw2, DR3 (DRβ1*1501)

Table 3. Correlation of HLA-DR Specificities with the Results of Antibiotic Therapy in 60 Patients with Lyme Arthritis.

SPECIFICITY	RESPONDERS (N = 22)	NONRESPONDERS (N = 38)
	number (percent)	
HLA-DR1	6 (27)	7 (18)
HLA-DR2	8 (36)	13 (34)
HLA-DR3	4 (18)	9 (24)
HLA-DR4	2 (9)	20 (53)*
HLA-DR5	6 (27)	6 (16)
HLA-DRw6	1 (5)	4 (11)
HLA-DR7	4 (18)	6 (16)
HLA-DR2 or HLA-DR4	10 (45)	23 (61)
HLA-DRw32	10 (45)	15 (39)
HLA-DRw33	7 (32)	18 (47)
HLA-DQw1	13 (59)	16 (42)
HLA-DQw2	6 (27)	8 (21)
HLA-DQw3	8 (36)	21 (55)

*P = 0.01 for the comparison with the patients in whom the arthritis responded to treatment.

known, however, whether encephalomyelitis has an immunogenetic basis.

It is of great interest that both chronic Lyme arthritis and rheumatoid arthritis are associated with the presence of HLA-DR4.²¹ However, only certain subtypes of HLA-DR4 — those encoded by the Dw4, Dw14, and Dw15 alleles — are found in patients with rheumatoid arthritis, whereas two other subtypes, HLA-Dw10 and Dw13, are not.¹³ The former group of subtypes differs from the latter primarily by the presence of negatively charged amino acids at position 70, 71, or 74 in the third diversity (hypervariable) region of the HLA-DR β 1 chain.^{21,22} Rheumatoid arthritis has a secondary association with the presence of HLA-DR1. Since HLA-DR1 has the same amino acid sequence as HLA-Dw4, Dw14, and Dw15 in the third diversity region, this unique alpha-helical structure has been postulated to specify the molecular basis for susceptibility to rheumatoid arthritis.^{21,22}

Of the five patients with chronic Lyme arthritis in whom nucleotide-sequence typing was done, three had the common northern European white HLA-Dw4 or Dw14 allele, as is found in patients with rheumatoid arthritis. Although the fourth patient had the HLA-Dw13 allele, which is not associated with rheumatoid arthritis, this patient was heterozygous (HLA-DR4, DR2), and it is possible that the HLA-Dw2 allele could independently account for his susceptibility to chronic Lyme arthritis. The fifth patient had only HLA-Dw2 as the allele putatively responsible for chronic joint involvement. Although more than one HLA conformation may be important in chronic Lyme arthritis, the lack of an association with HLA-DR1 suggests that the conformation of the third diversity region that confers susceptibility to rheumatoid arthritis is not critical to the development of chronic Lyme arthritis.

In five of the patients with chronic Lyme arthritis, HLA-DR4 occurred together with HLA-DR3, a combination that is reminiscent of that seen in insulin-dependent juvenile diabetes, in which the relevant susceptibility structure is thought to be located on the HLA-DQ molecule.²³ Arguing against a similarity in the molecular basis of susceptibility to these two diseases is the increased frequency of HLA-DR2 in Lyme arthritis and the fact that both of the patients with Lyme arthritis whom we tested had the Dw2 allele of HLA-DR2, which is associated with dominant resistance to insulin-dependent diabetes.

In patients with Lyme arthritis, only HLA-DR4 was significantly associated with a lack of response to antibiotic therapy. Since the frequency of treatment failure was not significantly increased in patients with the HLA-DR2 specificity, even after the exclusion of HLA-DR4-positive patients from the analysis, it is possible that the molecular basis of susceptibility may not be the same for both specificities. A recent report suggested that *B. burgdorferi* might trigger Reiter's syndrome or sacroiliitis, which did not respond to antibiotics, primarily in HLA-B27-positive patients.²⁴ Although 3 of the 28 patients with chronic arthritis in our study had HLA-B27, none had spondyloarthropathy, and the frequency of this specificity was not greater than one would expect in the general population.

On the basis of these results, several alternative mechanisms can be postulated for the development of chronic Lyme arthritis in genetically susceptible persons. First, the Class II molecules of the HLA-DR4 or DR2 haplotype may combine with a distinct arthritogenic epitope of *B. burgdorferi* that has molecular mimicry with a component of the host. The interaction of T helper cells with this major histocompatibility complex may lead to an autoimmune response that continues for some time after the organism has been killed. Second, as a result of thymic selection, the Class II molecules may have chosen potentially autoreactive T-cell clones that can be triggered by a spirochetal peptide that functions as a superantigen.²⁵ Conversely, during thymic maturation, these patients may have deleted T-cell clones necessary for the elimination of the spirochete. They may thus have persistent spirochetal infection accompanied by an ineffective immune response that causes "bystander" injury to the host. Because the causative agent of Lyme arthritis is known, this disease presents an important opportunity to determine the molecular interactions among the components of *B. burgdorferi*, specific Class II major histocompatibility molecules, and T-cell receptors that, in particular untoward combinations, lead to this form of chronic arthritis.

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